Articles

Application of Palladium(0)-Catalyzed Processes to the Synthesis of Oxazole-Containing Partial Ergot Alkaloids

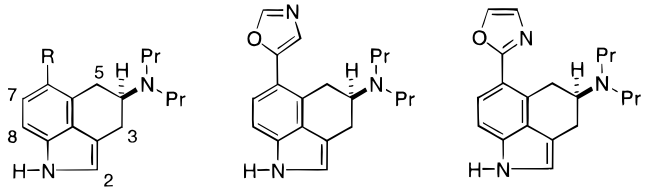
Benjamin A. Anderson,* Lisa M. Becke, Richard N. Booher,‡ Michael E. Flaugh,‡ Nancy K. Harn, Thomas J. Kress, David L. Varie, and James P. Wepsiec

Lilly Research Laboratories, A Division of Eli Lilly and Company, Chemical Process Research and Development Division and Neuroscience Discovery Research, Indianapolis, Indiana 46285-4813

Received February 27, 1997[⊗]

Syntheses of the potent 5-HT_{1A} agonists **2** and **3** were accomplished in several steps from the 6-iodo partial ergoline alkaloid **8**. Disparate tactics available for construction of differentially substituted oxazoles led to the development of new and general methodology critical to the efficient preparations of **2** and **3**. A novel palladium(0)- and copper(I)-cocatalyzed cyanation reaction provided efficient access to the nitrile **10**, a key intermediate in the synthesis of **2**. A palladium(0)-catalyzed cross-coupling reaction of **16** with oxazol-2-ylzinc chloride formed the potent 5-HT_{1A} agonist **3**.

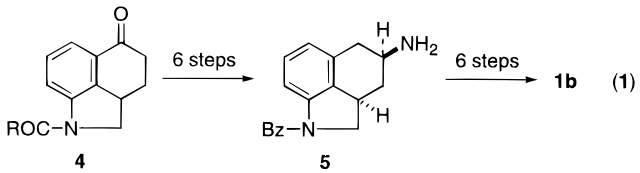
When appropriately substituted at the 6-position, the partial ergolines **1** are potent serotonin agonists at the 5-HT_{1A} receptor. Among the earliest examples of these agents are the 6-methoxy compound **1a** and the 6-carboxamido compound **1b**.[1] Later, 6-acyl derivatives such as **1c** were also found to have powerful serotonergic activity. Extensive pharmacological studies on both **1b** and **1c** have been conducted.[2] More recently, derivatives containing various heterocyclic functionalities at the 6-position were identified which exhibit strong serotonergic activity.[3] Connection of an oxazole either through its 5 or 2 position to the partial ergot alkaloid framework led to compounds **2** and **3**, both of which exhibit particularly interesting 5-HT_{1A} agonist activity.



1a, R = OMe
1b, R = $CONH_2$
1c, R = COMe

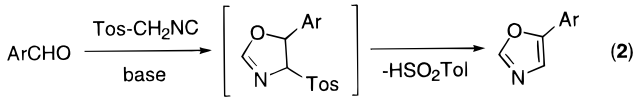
2 **3**

The clinical potential of the oxazolyl ergoline derivatives prompted our investigation into the development of efficient preparation of the two drug candidates, **2** and **3**. Substituted tricyclic partial ergolines **1** have been prepared from the Kornfeld−Woodward ketone **4** (eq 1).[2a,4] Lilly workers have recently reported an enantiospecific synthesis of **5**, a key indoline precursor to optically pure **1b**.[4a,b] With access to **5** thus provided, our efforts focused on the selective functionalization of this advanced intermediate. The development of new methodology proved critical to the efficient preparations of **2** and **3**. Most notably, we were challenged with adapting key palladium(0)-catalyzed coupling processes to ensure safe and reproducible production of the desired targets.



4 **5** (1)

The strategies required to produce the structurally similar candidates **2** and **3** were governed by the disparate methodologies available for construction of the two oxazoles.[5] 5-Aryl oxazoles may be prepared by the condensation of an aryl aldehyde with tosylmethyl isocyanide (TosMIC) (eq 2).[6] This reaction was expected to serve as a key step in the synthesis of **2**; however, this methodology does not accommodate the preparation of 2-substituted oxazoles such as **3**. Preliminary experiments indicated that related cyclodehydration strategies would also be ineffective for the synthesis of **3** (eq 3).[7] The convergent cross-coupling approach detailed herein was therefore pursued (eq 4). Despite these strategic differences, a parallel development of **2** and **3** demanded



(2)

‡ Neuroscience Discovery Research.

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) (a) Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. *J. Med. Chem.* **1988**, *31*, 1746. (b) Kruse, L. I.; Meyer, M. D. *J. Org. Chem.* **1984**, *49*, 4761.

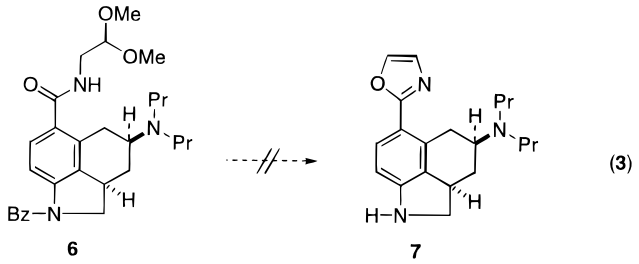
(2) (a) Foreman, M. M.; Fuller, R. W.; Leander, J. D.; Wong, D. T.; Nelson, D. L.; Calligaro, D. O.; Swanson, S. P.; Lucot, J. B.; Flaugh, M. E. *J. Pharmacol. Exp. Ther.* **1993**, *260*, 51. (b) Foreman, M. M.; Fuller, R. W.; Rasmussen, K.; Nelson, D. L.; Calligaro, D. O.; Zhang, L.; Barrett, E.; Booher, R. N.; Paget, C. J., Jr.; Flaugh, M. E. *J. Pharmacol. Exp. Ther.* **1994**, *270*, 1270.

(3) Booher, R. N.; Flaugh, M. E.; Lawhorn, D. E.; Martinelli, M. J.; Paget, C. J., Jr.; Schaus, J. M. U.S. Patent 5 347 013, 1994.

(4) (a) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30*, 3953. (b) Martinelli, M. J.; Leanna, M. R.; Varie, D. L.; Peterson, B. C.; Kress, T. J.; Wepsiec, J. P.; Khau, V. V. *Tetrahedron Lett.* **1990**, *31*, 7579. (c) Carr, M. A.; Creviston, P. E.; Hutchison, D. R.; Kennedy, J. H.; Khau, V. V.; Kress, T. J.; Leanna, M. R.; Marshall, J. D.; Martinelli, M. J.; Peterson, B. C.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8640. (d) For a synthesis utilizing a synthon other than the Kornfeld−Woodward ketone, see ref 1b.

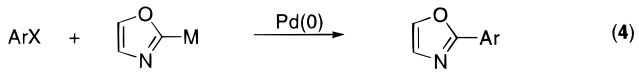
(5) (a) Turchi, I. J. In *Heterocyclic Compounds*; Turchi, I. J., Ed.; Wiley & Sons: New York, 1986; Vol. 45, Chapter 1. (b) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev. (Washington, D.C.)* **1974**, *75*, 389−437.

S0022-3263(97)00374-5 CCC: $14.00



(3)

the identification of an advanced intermediate that could be employed in the preparation of both targets.



(4)

Results and Discussion

Synthesis of the 5-Oxazole Derivative 2. As illustrated above (eq 2), preparation of the 5-oxazole derivative **2** employing a condensation reaction with TosMIC required access to the corresponding carboxaldehyde **13**. Preparation of **13** was accomplished in six steps from the optically active intermediate **5** in 35% overall yield (Scheme 1). Selective C-6 iodination of **5** was accomplished originally by use of *N*-iodosuccinimide (NIS). The combination of I_2 and H_5IO_6 in a water−acetic acid−sulfuric acid solution proved more desirable for application on multikilogram scale.[8] *N*-Propyl iodide and potassium carbonate readily effected double alkylation of the primary amine **8**. The alkylation reaction was allowed to progress to the point at which slight quantities of quaternized nitrogen were generated. Otherwise, purification difficulties were encountered due to contamination by small amounts of the monoalkylated product. This protocol significantly simplified product purification since the tetra-*n*-propylammonium species was easily removed by aqueous washes.

The indoline **10** has been prepared by cyanation of the 6-bromo derivative analogous to **9** employing Rosenmund−von Braun conditions (CuCN, NMP, 200 °C, 76%).[4b] High reaction temperatures, copper waste, and moderate yields led us to consider an alternate protocol. We chose to evaluate a transition metal-catalyzed process. Complete conversion of **9** to **10** was accomplished employing the Sekiya−Ishikawa protocol (KCN, Pd(PPh_3)$_4$, THF, reflux),[9] furnishing the desired product under moderate conditions but with inconsistent reaction rates (12−48 h).

A variety of modifications designed to improve the limited scope and modest reliability of cyanation reactions catalyzed by tetrakis(triphenylphosphine)palladium(0) have been reported.[10] Oxygen sensitivity of the catalyst was implicated as the source of reproducibility problems in the present case. When conducted under a nitrogen atmosphere but in solvents that were not previously deoxygenated, cyanation of **9** proceeded at the inconsistent rates described above. Less than 10% conversion occurred when a deoxygenated solvent was employed; however, brief introduction of a subsurface purge of air into the reaction mixture initiated the transformation. When conducted in solvent that had been presaturated with oxygen, cyanation of **9** was complete within 24 h.[11] To our knowledge, this sensitivity of the Pd(PPh_3)$_4$-catalyzed cyanation reaction to oxygen has not been previously reported.[12] We postulate that oxygen served to enhance the activity of the catalyst and/or catalyst precursor by oxidatively depleting inhibitory quantities of the triphenylphosphine ligand. Similar initiating effects by oxygen have been reported for related palladium(0)-catalyzed cross-coupling processes.[13]

Catalytic amounts of CuI are reported to enhance reaction rates of the Stille reaction, in part by competing with palladium for the phosphine ligands.[14] We considered addition of CuI a more controlled method for catalyst modification than introduction of oxygen. Iodide **9** was converted to **10** in 3 h when the reaction was conducted in deoxygenated solvent employing 5 mol % of Pd(PPh_3)$_4$ and 10 mol % of CuI in 67% yield after recrystallization (Table 1).[15] Small quantities of **11** (<2%) were sometimes observed and represented the only detectable side product generated in the reaction. Conversion to **10** was not observed when the reaction was carried out in the absence of the palladium catalyst (KCN, 10 mol % of CuI, THF, reflux).[16] The accelerating effect of copper salts on palladium(0)-catalyzed cyanation appears to be general and is currently being evaluated in greater detail.

Deprotection of **10** was typically conducted on unpurified material by hydrolysis with sodium hydroxide in ethanol to give **11** in 97% yield from **9**. Analytically pure indoline was separated from the contaminating species, benzoate and triphenylphoshine, by extraction with 1 N HCl. Manganese dioxide oxidized **11** to **12** in 70% yield.[4b,c,17] Treatment of **12** with DIBALH provided **13** in 90% yield. Reaction of **13** with TosMIC and 3 equiv of sodium methoxide in refluxing methanol for 5 h provided the desired oxazole **2** in 81% yield.

(6) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 2369.

(7) None of the typical reagent combinations (e.g. PBr_3, PI_3, TMSOTf) effected cyclodehydration of the hemiacetal precursor **6** to the oxazole product **7**. This observation is consistent with literature precedent that suggests such strategies are typically problematic for the preparation of 4,5-unsubstituted oxazoles (ref 5). For an exception, see: Moeller, H. German Patent 4 233 771, 1994.

(8) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128.

(9) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277.

(10) (a) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887. (b) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. (c) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1986**, *51*, 4714. (d) Davison, J. B.; Peerce-Landers, P. J.; Jasinski, R. J. *J. Electrochem. Soc.* **1983**, *130*, 1862. (e) Prochazka, H.; Siroky, M. *Collect. Czech. Chem. Commun.* **1983**, *48*, 1765.

(11) Triphenylphosphine oxide was observed in the reaction mixtures by HPLC only in cases where the cyanation reaction was successful.

(12) Decreased yields have been reported for cyanation reactions employing [^{11}C]KCN and aged, dilute solutions of Pd(PPh_3)$_4$. Andersson, Y.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1395.

(13) Farina, V.; Roth, G. P. *Adv. Met.-Org. Chem.* **1996**, *5*, 1−53.

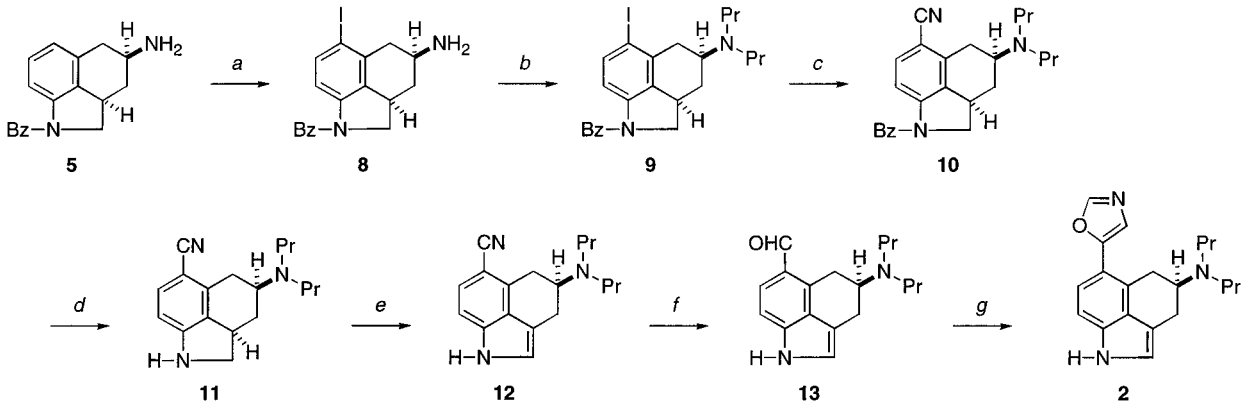
(14) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(15) The use of excess CuI in the presence of crown ethers has been reported to be beneficial to the tetrakis(triphenylphosphine)palladium(0)-catalyzed cyanation reactions of bromopyrazines: Sato, N.; Suzuki, M. *J. Heterocycl. Chem.* **1987**, *24*, 1371. This protocol does not circumvent purification problems associated with liberation of the product from the metal waste.

(16) Aryl halides have been converted to the corresponding aryl nitriles using KCN and catalytic CuI but at high reaction temperatures over extended time periods. Carr, R. M.; Cable, K. M.; Wells, G. N.; Sutherland, D. R. *J. Labeled Compd. Radiopharm.* **1994**, *34*, 887.

(17) Preparation of **12** was also accomplished by dehydration of **1b** ($POCl_3$, CH_3CN, >95%).

Scheme 1[a]



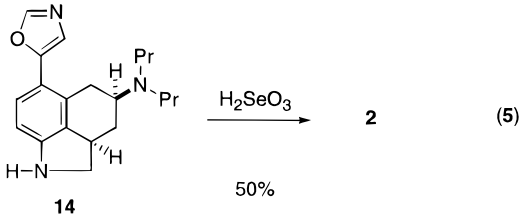
[a] Key: (a) I_2, H_5IO_6, H_2O, AcOH, H_2SO_4 (90%); (b) K_2CO_3, *n*-PrI, CH_3CN (83%); (c) KCN, $Pd(PPh_3)_4$, CuI, THF; (d) NaOH, EtOH (97%); (e) MnO_2, AcOH[4b] (70%); (f) DIBALH, toluene (90%); (g) NaOMe, TosMIC, MeOH (81%).

Table 1. Effect of CuI on Cyanation Reaction[a]

iodide	product	addend	time, h	% convn[b]
9	**10**	10 mol % of CuI	3	100
9	**10**	none	12−48	100
16	**12**	10 mol % of CuI	3	100
16	**12**	none	20	~25

[a] 2 equiv of KCN, 5 mol % of $Pd(PPh_3)_4$, THF. [b] Calculated using uncorrected HPLC values.

The optimal point for oxidation of the indoline to indole was given careful consideration. The nature of the substituent at the 6 position significantly influences the efficiency of this oxidation. Preliminary experiments evaluated the option of oxidizing the indoline **14** after installation of the oxazole group. Oxidation of **14** was accomplished by use of selenous acid in 50% yield (eq 5).

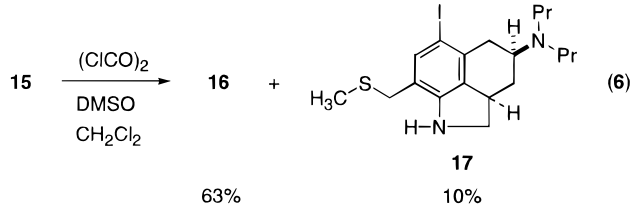


The reaction was only moderately successful, and the selenous acid was considered unacceptable because of contamination concerns. Other methods, such as MnO_2 or Pd/C, were either ineffective or complicated by competing reactions. Therefore, installation of the oxazole group after oxidation as described above was preferred.

Although a reliable route to **2** was established, strategic issues prompted further refinement since maximal overlap of synthetic steps common to production of **2** and **3** was not achieved. Conducting the cyanation reaction prior to conversion to the desired indole was a costly divergence since a related oxidation would also need to be accomplished in the synthesis of **3**. The sequence described in Scheme 1 was modified to effect deprotection and oxidation prior to cyanation (Scheme 2). This transposition of steps represents two strategic advantages. Most notably, **16** is the most desirable coupling partner for the convergent cross-coupling approach to the preparation of **3**. The revision would also have the beneficial effect of reducing the molecular weight of material forward processed in the synthesis of **2** by early stage cleavage of the *N*-benzoyl protecting group.

Literature precedent suggested the possibility of converting the protected indoline **9** directly to the indole **16** in one step.[18] Employing similar conditions (*t*-BuOK/H_2O/THF), formation of **15** and **16** was observed by HPLC although **16** was only a minor product (15%). The debenzoylation and indoline oxidation were therefore effected in two steps (Scheme 2). Deprotection of **9** was accomplished by treatment with sodium hydroxide in ethanol. Oxidation with manganese dioxide in dichloromethane (23 °C, 24 h) provided a 92% yield of **16**.

Alternatives to the MnO_2 oxidation were explored since eliminating the copious metal waste was desirable. Several methods (e.g. DDQ, chloranil, DMSO/oxalyl chloride) accomplished the transformation with variable success. Swern conditions were considered most advantageous owing to the efficiency of the reaction and the water solubility of the byproducts. The low-temperature DMOS/oxalyl chloride protocol provided the desired oxidation product **16** in 63% yield but was complicated by a competing electrophilic aromatic substitution reaction which led to the production of **17** in 10% yield (eq 6).[19]



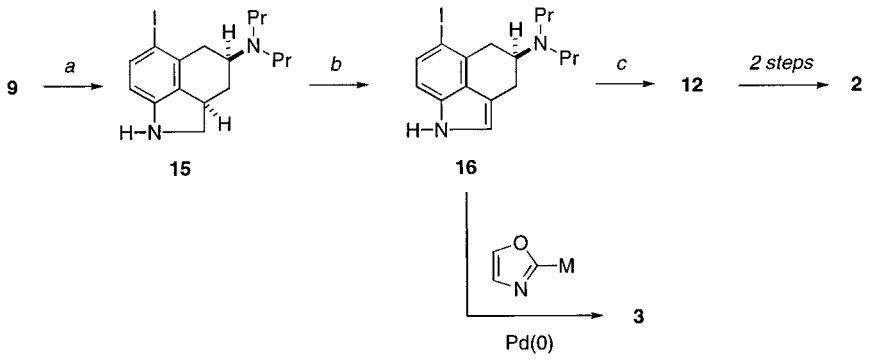
Interception of the original synthetic route was accomplished by a palladium(0)-catalyzed cyanation reaction of **16**. The accelerating effect of cocatalytic CuI was once again demonstrated as complete conversion to **12** was accomplished within 3 h (Table 1). A cyanation reaction conducted under identical conditions without CuI resulted in only ~25% conversion after 20 h. Preparation of **2** from **5** via the intermediate **16** was achieved in seven steps and in 48% overall yield.

Synthesis of the 2-Oxazole Derivative 3. In our parallel development of **2** and **3**, we envisioned **16** as a critical intermediate in the preparation of both targets. While **16** effectively provided access to **2**, the intermediate also proved advantageous in a convergent preparation of **3** (Scheme 2). The oxazole substituent was introduced

(18) Rebek, J.; Tai, D. F.; Shue, Y.-K. *J. Am. Chem. Soc.* **1984**, *106*, 1813.

(19) Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1660.

Scheme 2[a]



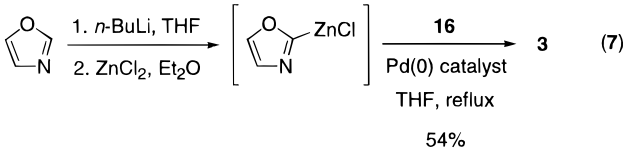
[a] Key: (a) NaOH, EtOH (78%); (b) MnO_2, CH_2Cl_2 (92%); (c) KCN, 5 mol % of $Pd(PPh_3)_4$, 10 mol % of CuI, THF (89%).

directly onto the partial ergot framework by a cross-coupling reaction of **16** with a suitably activated oxazole.

Trialkyltin derivatives of substituted oxazoles can be successfully coupled to aryl iodides in the presence of $Pd(PPh_3)_4$.[20] A brief examination of this reaction (eq 4: ArX = **16**; M = $SnBu_3$) demonstrated the viability albeit a clear need for optimization. Despite the modest yield of the reaction (11%), the most serious concern was the generation of stoichiometric quantities of trialkyltin byproducts. The potential for toxic alkyltin contamination of the final product ultimately precluded its use.[21]

The palladium(0)-catalyzed coupling of a zinc derivative was investigated as an alternative. Cross-coupling reactions of organozinc reagents are well-known and have been demonstrated to accommodate functionalities such as acidic amides.[22] Functional group compatibility was an important consideration given the presence of the unprotected indole nitrogen present in **16**.

In the event, oxazol-2-ylzinc chloride was prepared by the addition of excess zinc chloride to a solution of oxazol-2-yllithium.[23] Indole **16** was added to the resulting mixture along with the palladium(0) catalyst prepared from $Cl_2Pd(PPh_3)_2$/2 equiv of *n*-BuLi (eq 7).[24] Conversion



to the desired product **3** was accomplished after 1 h (THF, reflux) in 54% yield. No improvement in yield was achieved when excess oxazol-2-ylzinc chloride was employed. Not only did this one-pot method eliminate the potential of toxic alkyltin contamination of **3** but it circumvented the inconvenient isolation typically required of 2-stannyloxazoles.

The cross-coupling reaction of the oxazol-2-ylzinc chloride reagent developed for this synthesis has been investigated in detail by us and others, and the reagent was shown to be an efficient coupling partner with a variety of aryl halides, as well as aryl and vinyl triflates.[25] Oxazol-2-ylzinc derivatives have furthermore been demonstrated as useful intermediates for the preparation of 2-acyloxazole derivatives.[26]

The iodoindoline **9** reacted with oxazol-2-ylzinc chloride to give the oxazole product in 52% yield.[25a] Oxidation of the indoline with MnO_2 after debenzoylation afforded only 37% of the indole, further prompting development of the strategies summarized above.

Conclusion

We have developed syntheses of the potent 5-HT_{1A} agonists **2** and **3** utilizing **16** as an advanced intermediate common to both syntheses. Selective C-6 iodination of the partial ergot alkaloid **5** was accomplished in high yield, providing the precursor to **16**. A novel palladium(0)- and copper(I)-cocatalyzed cyanation reaction, which eliminated harsh reaction conditions and excessive copper waste, was developed to provide efficient and reproducible access to the key intermediate **12**. The desired 5-substituted oxazole **2** was produced by a condensation reaction employing tosylmethyl isocyanide.

In a generally valuable method for the C-2 elaboration of oxazoles, an organozinc derivative of the unsubstituted oxazole was coupled with **16** in the presence of a palladium(0) catalyst to provide the desired product **3**. The syntheses of both **2** and **3** were achieved by cross-coupling methodology and provided new insights into these fundamental processes. Not only should the methods reported here for the manipulation of partial ergot alkaloids provide a general strategy for the preparation of related pharmacologically active agents but the palladium(0)-catalyzed methodologies should find general application.

Experimental Section

All starting materials were commercially available, except for **5** which was prepared by the reported method.[4b] Oxazole may be prepared by the method of Brederick and Bangert.[27] Reactions were routinely performed under an inert atmosphere (N_2). Where noted, THF was deoxygenated by a subsurface N_2 purge for 1 h immediately prior to use. Evaporation of solvents was accomplished by rotary evaporation at 10−20 Torr.

(20) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693.
(21) Barnes, J. M.; Stoner, H. B. *Pharmacol. Rev.* **1959**, *11*, 211.
(22) (a) Knochel, P.; Singer, R. D. *Chem. Rev. (Washington, D.C.)* **1993**, *93*, 2117. (b) Erdik, E. *Tetrahedron* **1992**, *44*, 9577.
(23) Efforts to prepare and cross-couple the 2-boronic acid derivative of oxazole were unsuccessful.
(24) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.
(25) (a) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583. (b) Crowe, E.; Hossner, F.; Hughes, M. J. *Tetrahedron* **1995**, *51*, 8889.
(26) Harn, N. K.; Gramer, C. J.; Anderson, B. A. *Tetrahedron Lett.* **1995**, *36*, 9453.
(27) Bredereck, H.; Bangert, R. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 662.

1-Benzoyl-6-iodo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole-4-amine (8). H_2SO_4 (4.4 g, 45 mmol) was added dropwise to a solution of **5** (10 g, 36 mmol) in 1:1 acetic acid/water (50 mL). Periodic acid (2.2 g, 9.6 mmol) and I_2 (4.8 g, 18.9 mmol) were added in rapid succession. The solution was heated at 60 °C for 1 h. With vigorous agitation, a 20% $NaHSO_3$ solution (10 mL) was added to the warm mixture. After the solution was cooled with an ice bath, CH_2Cl_2 (50 mL) was added and the pH adjusted to 12 with a 10 N NaOH solution (60 mL). The two-phase mixture was warmed to rt, and CH_2Cl_2 (50 mL) was added. The organic layer was isolated, and the aqueous layer was extracted once with CH_2Cl_2. The extracts were combined and dried over anhydrous Na_2SO_4. CH_3CN (70 mL) was added, and a solvent exchange to CH_3CN was affected. A mixture with a yellow precipitate resulted, and it was cooled at −15 °C overnight. The mixture was filtered cold, and the solid was rinsed twice with cold CH_3CN (30 mL). Then 13.1 g (90% yield) of **8** was obtained: mp 178−180 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 7 H), 4.27 (broad s, 1 H), 3.70 (t, J = 15 Hz, 1 H), 3.30 (m, 2 H), 3.05 (dd, J = 17 Hz, J = 6 Hz, 1 H), 2.18 (m, 2 H), 1.30 (q, J = 12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 141.8, 137.7, 136.8, 136.2, 136.2, 134.5, 130.8, 128.6, 127.4, 115.9, 92.4, 58.1, 49.2, 42.8, 38.1, 36.8; MS m/z 404 (M^+). Anal. Calcd for $C_{18}H_{17}IN_2O_2$: C, 53.48; H, 4.24; N, 6.93. Found: C, 53.20; H, 4.11; N, 6.64.

1-Benzoyl-1,2,2a,3,4,5-hexahydro-6-iodo-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (9). The primary amine **8** (100 g, 0.25 mol), potassium carbonate (137 g, 1.0 mol), and 1-iodopropane (97 mL, 1.0 mol) were slurried together in CH_3CN (1 L). The heterogeneous reaction mixture was warmed to approximately 75 °C and stirred for 17 h. The mixture was cooled to room temperature, and water (500 mL) and *tert*-butyl methyl ether (500 mL) were added. The organic layer was separated and washed with water. CH_3CN (500 mL) was added to the organic layer, and the volume was reduced in half by evaporation. A small amount of precipitated black solids was removed by hot gravity filtration. The filtrate was cooled to rt, and orange crystals formed. The mixture was filtered cold, and the solid was rinsed twice with cold CH_3CN (75 mL). **9** (100 g, 83% yield) was obtained: mp 109−110 °C; IR (KBr) 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 7 H), 4.28 (broad s, 1 H), 3.66 (t, J = 11.0 Hz, 1 H), 3.34 (m, 1 H), 3.20 (m, 1 H), 2.81 (dd, J = 6 Hz, J = 18 Hz, 1 H), 2.47 (m, 5 H), 2.16 (m, 1 H), 1.38 (m, 5 H), 0.91 (t, J = 7 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 141.7, 137.9, 137.6, 137.6, 136.3, 130.7, 128.6, 127.4, 106.8, 93.3, 58.0, 52.9, 38.5, 35.1, 29.1, 22.6, 11.9; MS m/z 488 (M^+). Anal. Calcd for $C_{24}H_{29}IN_2O$: C, 59.02; H, 5.99; N, 5.74. Found: C, 59.03; H, 5.87; N, 5.64.

1-Benzoyl-6-cyano-1,2,2a,3,4,5-hexahydro-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (10). The iodide **9** (0.63 g, 1.29 mmol), pulverized anhydrous KCN (0.092 g, 1.42 mmol), $Pd(PPh_3)_4$ (0.075 g, 0.065 mmol), and CuI (0.024 g, 0.126 mmol) were placed in a flask which was maintained under vacuum for 1 h. After the solution was flushed with N_2, deoxygenated THF (6.5 mL) was added via syringe. The resulting mixture was refluxed under N_2 for 3 h. After the solution was cooled to rt, EtOAc (30 mL) was added and the mixture was filtered through Celite. The filtrate was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to an oil (0.57 g, 114% recovery). Compound **10** was typically used directly in the next step without purification. An analytically pure sample was prepared by recrystallization from isopropyl alcohol to yield a gray solid (67% yield): mp 110−111 °C; IR (KBr) 2212, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 7 H), 4.34 (m, 1 H), 3.72 (t, J = 11.1 Hz, 1 H), 3.33 (m, 1 H), 3.25 (m, 1 H), 3.13 (m, 1 H), 2.74 (dd, J = 10 Hz, J = 18 Hz, 1 H), 2.47 (m, 4 H), 2.28 (m, 1 H), 1.47 (m, 5 H), 0.90 (t, J = 7 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 145.4, 138.7, 136.1, 134.6, 133.7, 131.6, 129.1, 127.8, 118.1, 114.3, 106.7, 58.9, 57.2, 53.1, 38.1, 29.7, 28.1, 22.9, 12.2; MS m/z 283 (M^+). Anal. Calcd for $C_{18}H_{25}N_3$: C, 77.48; H, 7.54; N, 10.84. Found: C, 77.55; H, 7.49; N, 10.74.

6-Cyano-1,2,2a,3,4,5-hexahydro-*N*,*N*-dipropylbenz[*cd*]-indole-4-amine (11). A 5 N NaOH solution (5 mL, 25 mmol) was added to a solution of unpurified **10** (5 g) in EtOH (50 mL). The mixture was heated at reflux for 30 min. After the solution was cooled to rt, the solvent was evaporated. The resulting solid was dissolved in *tert*-butyl methyl ether (100 mL), and the solution was washed with water. The product was extracted from the organic phase with 1 N HCl solution. The acidic phase was neutralized with a 5 N NaOH solution and then extracted with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give 3.7 g of **11** as a pale orange solid (≥97% yield): mp 115−116 °C; IR (KBr) 2210 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz, 1 H), 6.41 (d, J = 8.1 Hz, 1 H), 4.17 (s, 1 H), 3.77 (t, J = 7.4 Hz, 1 H), 3.22 (m, 3 H), 3.05 (dd, J = 6.2, 17.8 Hz, 1 H), 2.66 (m, 1 H), 2.48 (m, 4 H), 2.22 (m, 1 H), 1.47 (m, 5 H), 0.91 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.1, 137.4, 134.0, 130.8, 119.3, 105.8, 99.5, 57.4, 55.8, 52.8, 38.9, 29.6, 27.5, 22.6, 11.9; MS m/z 283 (M^+). Anal. Calcd for $C_{18}H_{25}N_3$: C, 76.28; H, 8.89; N, 14.82. Found: C, 76.65; H, 9.11; N, 14.75.

1,2,2a,3,4,5-Hexahydro-6-iodo-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (15). To a slurry of the indoline **9** (10 g, 20.5 mmol) in EtOH (100 mL) was added a 5 N NaOH solution (41 mL, 205 mmol). The mixture was refluxed for 2 h, and the resulting solution was allowed to cool to rt overnight. The EtOH was evaporated, and EtOAc (150 mL) was added. The solution was washed with water, dried over anhydrous Na_2SO_4, and evaporated to give a brown gum (7.5 g). Chromatography on silica gel (EtOAc) yielded 6.2 g (78%) of **15** as a brown oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 1 H), 6.27 (d, J = 8.0 Hz, 1 H), 3.66 (m, 2 H), 3.14 (m, 3 H), 2.76 (m, 2 H), 2.43 (m, 4 H), 2.15 (m, 2 H), 1.48 (m, 4 H), 0.91 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 150.5, 137.1, 132.6, 108.9, 85.8, 60.6, 58.5, 56.0, 52.9, 39.9, 34.6, 29.3, 22.6; MS m/z 384 (M^+). Anal. Calcd for $C_{17}H_{25}IN$: C, 53.13; H, 6.56; N, 7.29; I, 33.02. Found: C, 53.34; H, 6.47; N, 7.35; I, 33.00.

6-Iodo-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (16). A solution of the indoline **15** (78.0 g, 0.2 mol) in CH_2Cl_2 (1 L) was stirred with MnO_2 (100 g, 1.15 mol) for 24 h. The mixture was vacuum filtered through Celite. Chromatography on a Prep 500 column using toluene, then 3% EtOAc in toluene, and ending with 5% EtOAc in toluene yielded 71.9 g (92%) of **16** as an orange oil.

Alternate Synthesis. To a solution of oxalyl chloride (0.28 g, 2.2 mmol) in CH_2Cl_2 (2 mL) at −60 °C was added via syringe DMSO (0.34 g, 4.4 mmol) in CH_2Cl_2 (0.6 mL). After 5 min, indoline **15** (0.76 g, 2.0 mmol) in CH_2Cl_2 (1 mL) was added via syringe. After 10 min, triethylamine (1.0 g, 9.9 mmol) was added. The cold bath was removed and the mixture allowed to warm to rt. Water (4 mL) was added, the organic layer was separated, and the aqueous was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and evaporated to give a brown oil (0.70 g). Chromatography on silica gel (4:1 hexane/EtOAc) yielded 0.48 g (64%) of **16** and 0.09 g (10%) of **17**.

16: ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (broad s, 1 H), 7.46 (d, J = 8.4 Hz, 1 H), 6.94 (d, J = 8.4 Hz, 1 H), 6.82 (s, 1 H), 3.26 (m, 1 H), 2.91 (m, 4 H), 2.59 (m, 4 H), 1.51 (m, 4 H), 0.92 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 133.2, 131.7, 128.6, 118.1, 113.8, 110.5, 85.5, 58.9, 53.1, 34.6, 24.5, 22.5, 11.9; MS m/z 382 (M^+). Anal. Calcd for $C_{17}H_{23}IN_2$: C, 53.41; H, 6.06; N, 7.33. Found: C, 53.37; H, 5.96; N, 7.19.

17: ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1 H), 4.28 (broad s, 1 H), 3.72 (s, 1 H), 3.55 (q, J = 13.5, 46.6 Hz, 2 H), 3.16 (m, 3 H), 2.73 (m, 2 H), 2.42 (m, 4 H), 2.16 (m, 2 H), 1.98 (s, 3 H), 1.49 (m, 4 H), 0.91 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 137.5, 135.8, 132.8, 118.2, 85.3, 58.6, 55.9, 52.9, 39.9, 34.4, 29.3, 22.5, 14.8, 11.8; MS m/z 444 (M^+).

6-Cyano-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (12). Iodide **16** (0.40 g, 1.04 mmol), pulverized anhydrous KCN (0.13 g, 2.0 mmol), $Pd(PPh_3)_4$ (0.057 g, 0.049 mmol), and CuI (0.019 g, 0.099 mmol) were placed in a flask which was maintained under vacuum for 1 h. After the solution was flushed with N_2, deoxygenated THF (5 mL) was added via syringe. The resulting mixture was heated at 60 °C under N_2 for 3 h. After the solution was cooled to rt, EtOAc (25 mL) was added. The solution was washed with water, and the product was ex-

tracted from the organic phase with a 1 N HCl solution. The acidic phase was basified at 0 °C with a 5 N NaOH solution and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give 0.29 g of a light brown oil. Chromatography on silica gel (3:1 to 1:1 hexane/EtOAc) yielded 0.26 g (89%) of **12** as a yellow oil which crystallized upon standing: mp 109−110 °C; IR (KBr) 2219 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.34 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1 H), 6.97 (s, 1 H), 3.30 (m, 2 H), 3.02 (m, 2 H), 2.83 (m, 1 H), 2.59 (t, J = 7.3 Hz, 4 H), 1.51 (m, 4 H), 0.94 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 135.1, 126.9, 125.8, 119.5, 114.7, 109.3, 99.2, 58.4, 52.9, 28.4, 24.5, 22.5, 11.8; MS m/z 281 (M^+). Anal. Calcd for $C_{18}H_{23}N_3$: C, 76.83; H, 8.24; N, 14.93. Found: C, 76.78; H, 8.35; N, 14.94.

6-Formyl-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (13). A solution of the nitrile **12** (10 g, 35.6 mmol) in toluene (100 mL) was cooled to −58 °C, and DIBALH as a 1 M solution in toluene (71 mL, 71 mmol) was added dropwise over 2 h. Thirty minutes after addition was complete, cooling was removed and glacial acetic acid (20 mL) was added slowly to control foaming. Water (100 mL) was then slowly added, and the reaction mixture was stirred for 2 h. The aqueous layer was separated and treated with saturated Rochelle salt solution (50 mL) and EtOAc (100 mL). The pH was adjusted to 10 with a 5 N NaOH solution. The organic layer was separated, and the aqueous was extracted with EtOAc. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated to near dryness. Trituration with hexane gave **13** as a tan solid, 9.07 g (90% yield): IR (KBr) 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1 H), 9.44 (s, 1 H), 7.63 (d, J = 8.5 Hz, 1 H), 7.19 (d, J = 8.5 Hz, 1 H), 6.93 (s, 1 H), 3.83 (m, 1 H), 3.30 (m, 1 H), 3.06 (m, 2 H), 2.80 (t, J = 13.3 Hz, 1 H), 2.58 (m, 4 H), 1.51 (m, 4 H), 0.92 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 137.8, 137.0, 127.2, 125.7, 124.4, 119.7, 115.7, 109.1, 58.8, 53.2, 27.5, 24.2, 22.7, 12.0; MS m/z 284 (M^+). Anal. Calcd for $C_{18}H_{24}NO$: C, 76.02; H, 8.51; N, 9.85. Found: C, 76.25; H, 8.71; N, 9.71.

6-(5-Oxazoyl)-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (2). To a solution of the aldehyde **13** (20.0 g, 70.4 mmol) in MeOH (200 mL) was added NaOMe (12.8 g, 237 mmol) as a solid portionwise. After the solution was stirred for 5 min, tosylmethyl isocyanide (16.5 g, 84.5 mmol) was added as a solid portionwise. The resulting solution was refluxed for 5 h, after which water (100 mL) was added to the hot reaction mixture. After cooling to rt, the mixture was cooled at 0 °C and filtered. The solid was washed with cold 50% MeOH in water to afford 18.4 g (81%) of **2** as a tan solid. An analytically pure sample of **2** could be acquired by passing the material through a silica plug with EtOAc: mp 165−166 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 2 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 1 H), 7.19 (s, 1 H), 6.90 (s, 1 H), 3.25 (m, 2 H), 3.01 (m, 2 H), 2.82 (m, 1 H), 2.59 (m, 4 H), 1.49 (q, J = 7.2, 14.6 Hz, 4 H), 0.92 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 149.7, 133.6, 129.5, 127.1, 122.1, 121.8, 118.5, 115.9, 114.6, 108.8, 58.5, 53.1, 29.4, 23.8, 22.6, 11.9; MS m/z 323 (M^+). Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.33; H, 7.90; N, 13.19.

6-(2-Oxazoyl)-*N*,*N*-dipropylbenz[*cd*]indole-4-amine (3). To a solution of oxazole (0.10 mL, 1.45 mmol) in deoxygenated THF (10 mL) at −70 °C was added 1.6 M *n*-butyllithium in hexane (1.0 mL, 1.6 mmol). After 30 min, 1 M zinc chloride in ether (4.35 mL, 4.35 mmol) was added. The reaction mixture was warmed to 0 °C for 1 h after which a solution of the iodide **16** (0.55 g, 1.45 mmol) in deoxygenated THF (7 mL) was added. The palladium catalyst (prepared by the treatment of a suspension of $(Ph_3P)_2PdCl_2$ (51 mg, 0.073 mmol) in deoxygenated THF (5 mL) with 1.6 M *n*-butyllithium in hexane (0.09 mL, 0.145 mmol)) was added, and the resulting mixture was refluxed for 1 h. The final reaction mixture was diluted with EtOAc (20 mL) and was washed with brine and water. The organic solution was dried over anhydrous Na_2SO_4 and concentrated. Chromatography on silica gel (4:4:1 $CHCl_3$/hexane/MeOH) gave 0.25 g (54%) of **3** as a yellow oil: IR (film) 1611, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.12 (s, 1 H), 7.85 (d, J = 8.5 Hz), 7.71 (s, 1 H), 7.25 (d, J = 6.8 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 1 H), 6.86 (s, 1 H), 3.83 (dd, J = 2.7, 16.4 Hz, 1 H), 3.30 (m, 1 H), 3.17 (m, 1 H), 3.03 (m, 1 H), 2.84 (m, 1 H), 2.60 (m, 4 H), 1.52 (q, J = 7.3, 14.8 Hz, 1 H), 0.91 (t, J = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 137.6, 134.4, 132.2, 127.8, 127.1, 123.4, 118.4, 115.6, 116.2, 108.5, 58.7, 53.1, 29.3, 24.3, 22.6, 11.9; HRMS (M^+) calcd for $C_{20}H_{26}N_3O$ 324.2076, found 324.2074. Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 73.97; H, 7.84; N, 12.90.

Acknowledgment. David Marks is gratefully acknowledged for providing analytical support. We are also indebted to Bret Astleford and Robert Waggoner for valuable experimental contributions.

JO970374J